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PATENT Attorney Docket No.: 17726A-000420US

Assistant Commissioner for Patents

Washington, D.C. 20231

many 13, 2007

TOWNSEND and TOWNSEND and CREW LLP

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LEE et al.

Application No.: 10/028,726

Filed: December 21, 2001

For: PRODUCTS AND METHODS FOR CONTROLLING THE SUPPRESSION OF THE NEOPLASTIC PHENOTYPE

Examiner:

Not yet assigned

Art Unit:

1633

COMMUNICATION UNDER

37 C.F.R. §§ 1.821-1.825

AND

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents Washington, D.C. 20231

Sir:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, 37 C.F.R. §§ 1.821-1.825, mailed December 13, 2002, Applicants submit that the computer-readable form in the instant application is identical with that filed in Application No. 08/472,760, filed November 27,1996. In accordance with 37 C.F.R. § 1.821(e), please use the computer-readable form filed in Application No. 08/472,760 as the computer-readable form for the instant application. A paper copy of the last filed Sequence Listing from Application No. 08/472,760 is submitted herewith. The information in the paper copy of the Sequence Listing is identical to that which is in the computer readable form, as required under 37 C.F.R. § 1.821(f).

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It is understood that the Patent and Trademark Office will make the necessary changes in application number and filing date for the computer-readable form that will be used for the instant application.

Please amend the specification in adherence with 37 C.F.R. §§ 1.821-1.825 as follows.

In the Specification:

Please replace paragraph [152] beginning at page 27, line 15, with the following:

[152] --The hypothetical protein predicted from the nucleotide sequence was expected to have MW about 106 kD. The immunoprecipitated protein has a MW about 110-114 kD. The complete RB protein amino acid sequence (SEQ ID NO:2) is illustrated in Table 1. This complete sequence obtained from the newly reconstructed clone which contains the most 5' end stretch missing in the original cDNA clone Science, 235:1394-1399 (1987).

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TABLE 1

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MPPKTPRKTAATAAAAAEPPAPPPPPPEEDPE
                                               34)
QDSGPEDLPLVRLEFEETEEPDFTALCQKLKIPDHVRERA
                                               74)
WLTWEKVSSVDGVLGGYIQKKKELWGICIFIAAVDLDEMS
                                             (114)
FTFTELQKNIEISVHKFFNLLKEIDTSTKVDNAMSRLLKK
                                             (154)
YDVLFALFSKLERTCELIYLTQPSSSISTEINSALVLKVS
                                             (194)
WITFLLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML
                                             (234)
LKEPYKTAVIPINGSPRTPRRGQMRSARIAKOLENDTRII
                                             (274)
EVLCKEHECNIDEVKNVYFKNFIPFMNSLGLVTSNGLPEV
                                             (314)
ENLSKRYEEIYLKNKDLDARLFLDHDKTLQTDSIDSFETO
                                             (354)
RTPRKSNLDEEVNVIPPHTPVRTVMNTIQQLMMILNSASD
                                             (394)
QPSENLISYFNNCTVNPKESILKRVKDIGYIFKEKFAKAV
                                             (434)
GQGCVEIGSQRYKLGVRLYYRVMESMLKSEEERLSIONFS
                                             (474)
KLLNDNIFHMSLLACALEVVMATYSRSTSQNLDSGTDLSF
                                             (514)
PWILNVLNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE
                                             (554)
HRIMESLAWLSDSPLFDLIKOSKDREGPTDHLESACPLNL
                                             (594)
PLQNNHTAADMYLSPVRSPKKKGSTTRVNSTANAETQATS
                                             (634)
AFQTQKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP
                                             (674)
ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV
                                             (714)
KNIDLKFKIIVTAYKDLPHAVOETFKRVLIKEEEYDSIIV
                                             (754)
FYNSVFMQRLKTNILQYASTRPPTLSPIPHIPRSPYKFPS
                                             (794)
SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRILVS
                                             (834)
IGESFGTSEKFOKINOMVCNSDRVLKRSAEGSNPPKPLKK
                                             (874)
LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ
                                             (914)
KMNDSMDTSNKEEK
                                             (928)
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single-letter abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.--
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Please replace paragraph [153] beginning at page 27, line 15, with the following:

[153] --The amino acid sequence (Table 1; SEQ ID NO:2) is written in the abbreviation code recognized in the art. Single-letter abbreviations for the amino acid residues are: A = Alanine, C = Cysteine, D = Aspartic acid, E = Glutamic Acid, F = Phenylalanine, G = Glycine, H = Histidine, I = Isoleucine, K = Lysine, L = Leucine, M = Methionine, N =

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Asparagine, P = Proline, Q = Glutanine, R = Arginine, S = Serine, T = Threonine, V = Valine, W = Tryptophane and Y = Tyrosine.--

Please replace paragraph [225] beginning at page 27, line 15, with the following:

[225] --Pending U.S. patent application Serial No. 108,748 discloses and claims the RB gene and its clone. The RB gene and its clone had the nucleotide <u>and amino acid</u> sequences sequence depicted in <u>Table 4 Table 2 (SEQ ID NOS:1 and 2)</u>.

TABLE 4

TTCC	GGTT	TT	TCTCA	.GGG(A CC	STTGA	LTAA	TA	TTTC	AAT	CGGG	AGTO	GG C	SAGAC	GACGO	;	60
GGCG	TGCC	CC	GCGTC	CGCC	GC GC	CGTCC	TCCI	ccc	CCGGC	CGCT	CCTC	CCACA	AGC T	rcgci	rggcTc		120
CCGC	CGCG	GA ,	AAGGC	GTC	ATG	CCG	CCC	AAA	ACC	CCC	CGA	AAA	ACG	GCC	GCC		171
					Met	Pro	Pro	Lys	Thr	Pro	Arg	Lys	Thr	Ala	Ala		
					1				5					10			
7.00	~~~	aaa	G G T	aaa	aaa	aaa	CI N N		aaa.	CCA	ccc	CCC	CCG	CCG	CCC		219
ACC	GCC	GCC	GCT	GCC	GCC.	7.7.5	GAA	Dro	Dro	Ala	Dro	Dro	Dro	Dro	Dro		417
Thr	Ala	дта	Ala	Ата	Ата	Ата	GIU	20	PIO	Ата	PIO	PIO	25	PIU	FIO		
			15					20									
ССТ	ССТ	GAG	GAG	GAC	CCA	GAG	CAG	GAC	AGC	GGC	CCG	GAG	GAC	CTG	CCT		267
Pro	Pro	Glu	Glu	Asp	Pro	Glu	Gln	Asp	Ser	Gly	Pro	Glu	Asp	Leu	Pro		
		30					35					40					
CTC	GTC	AGG	CTT	GAG	TTT	GAA	GAA	ACA	GAA	GAA	CCT	GAT	TTT	ACT	GCA		315
Leu	Val	Arg	Leu	Glu	Phe	Glu	Glu	Thr	Glu	Glu	Pro	Asp	Phe	Thr	Ala		
	45					50					55						
		~~~			220	2 (11.2)	aar	CI N CII	C A TI	ama	707	CINC	אפא	CCT	тсс		363
1 TA	TGT	CAG	AAA	TTA	AAG	TIA	Dro	Aan	Uia	Wal	AGA	Glu	Aug	Ala	TGG		
	Cys	GIn	Lys	ьец	<u>ьув</u> 65	тте	PIO	Asp	птр	70	Arg	Gru	Arg	AIG	75		
_60					65				<del></del>								
тта	ACT	TGG	GAG	AAA	GTT	TCA	TCT	GTG	GAT	GGA	GTA	TTG	GGA	GGT	TAT		411
Leu	Thr	Trp	Glu	Lys	Val	Ser	Ser	Val	Asp	Gly	Val	Leu	Gly	Gly	Tyr		
				80					85					90			
ATT	CAA	AAG	AAA	AAG	GAA	.CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA		459
Ile	Gln	Lys	Lys	Lys	Glu	Leu	Trp		Ile	Cys	Ile	Phe	Ile	Ala	Ala		
w,			95					100					105				
	an a	OIII 3	GAT	CAC	א ידיכי	TICC	TTTC	y Carr	արոր	V Cur	GNC	СТА	CAG	ΔΔΔ	AAC		507
V21	AGE	LA	Asp	GAG	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lvs	Asn		
val	Asp	110		GIU	Met	JCI	115	TILL	1110		<u> </u>	120					-
		110	<u>'</u>					,									

PATENT LEE et al. Application No.: 10/028,726 Page 5 ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT 555 Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp 130 125 ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT 603 Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr 150 155 145 140 GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT 651 Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu 165 160 ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT 699 Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser 185 175 180 GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG 747 Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly 195 190 GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG 795 Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met 205 210 215 CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC 843 Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu 230 225 220 AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA 891 Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg 240 245 ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA 939 Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu 260 255 GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT 987 Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys 275 280 AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT 1035 Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe 290 295 ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA 1083 Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu 305 310 300 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA 1131 Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu 325 320

**PATENT** LEE et al. Application No.: 10/028,726 Page 6 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT 1179 Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser 340 335 ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT 1227 Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp 355 GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG 1275 Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met 375 370 AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA 1323 Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln 390 380 385 CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA 1371 Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro 400 405 AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC TTT AAA 1419 Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys 420 425 GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA 1467 Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser 430 435 CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC 1515 Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser 450 ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA 1563 Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys 465 470 CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT 1611 Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu 480 485 GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT 1659 Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp 500 495 TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA 1707 Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu 515 520 AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA 1755 Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu 530 535 525

**PATENT** LEE et al. Application No.: 10/028,726 Page 7 GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT 1803 Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His 550 540 545 CGA ATC ATG GAA TCC CTT GCA TGG CTC TCA GAT TCA CCT TTA TTT GAT 1851 Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp 560 565 CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA 1899 Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu 580 575 TCT GCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA 1947 Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala 595 590 GAT ATG TAT CTT TCT CCT GTA AGA TCT CCA AAG AAA AAA GGT TCA ACT 1995 Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Lys Gly Ser Thr 610 615 605 ACG CGT GTA AAT TCT ACT GCA AAT GCA GAG ACA CAA GCA ACC TCA GCC 2043 Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala 630 635 620 625 TTC CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTG TTT TAT 2091 Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr 645 640 AAA AAA GTG TAT CGG CTA GCC TAT CTC CGG CTA AAT ACA CTT TGT GAA 2139 Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu 660 655 CGC CTT CTG TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT 2187 Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu 675 680 TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT 2235 Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His 690 695 TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG 2283 Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys 700 705 710 AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT 2331 Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu 720 725 CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG 2379 Pro His Ala Val Gln Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu 735 740 GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA 2427

LEE et al. **PATENT** Application No.: 10/028,726 Page 8 Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg 755 CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG 2475 Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu 770 765 TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA 2523 Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser 790 785 780 795 CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG AAG AGT 2571 Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser 805 800 CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA 2619 Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro 815 820 AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG 2667 Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu 830 835 AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC 2715 Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu 845 850 AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA 2763 Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu 860 865 870 CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC 2811 Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu 885 880 CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT 2859 Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr 895 900 CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser 910 915 920 AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT 2962 Asn Lys Glu Glu Lys 925 2994 GGATTCATTG TCTCTCACAG ATGTGACTGT AT

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### TABLE 4

TTCCGCTTTT TCTCAGGGGA CGTTGAAATT ATTTTTGTAA CGGGAGTCGG GAGAGGACGG	
TTCCCCTTTT TCTCACCCCA CCTTCAAATT ATTTTTCTAA COCOACTCCC CACACCACCC	- 00
CCCTGCCCC CCCTCCCCCC CCCTCCTCCT CCCCCCCC	<del>120</del>
CCGCCGCGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC	<del>171</del>
Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala	
110	
	210
ACC GCC GCT GCC GCC GCG GAA CCC CCG GCA CCG CCG CCG	
<u>—————————————————————————————————————</u>	
CCT CCG TAG GAC GAC CCA GAG GAC AGC GGC CCG GAG GA	<del>267</del>
Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro	
303540	ř
CTC CTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA	- 315
Leu Val Arg Leu Glu Phe Glu Glu Thr Clu Glu Pro Asp Phe Thr Ala	
455055	
	262
TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG	- 363
Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp  60 75	•
-60 70	
TTA ACT TGG GAG AAA GTT TCA TCT GTG GAT GGA GTA TTG GGA GGT TAT	<del>411</del>
Leu Thr Trp Clu Lys Val Ser Ser Val Asp Cly Val Leu Cly Cly Tyr	
80 85 90	
ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA	459
Ile Cln Lys Lys Clu Leu Trp Cly Ile Cys Ile Phe Ile Ala Ala	
95 100 105	
CTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC	507
Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn  110 120	
110	
ATA CAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT	<del>555</del>
Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp	
$\frac{125}{130}$	
ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT	603
Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr	
140 145 150 150	
CAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT	<del> 651</del>
Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu	

**PATENT** LEE et al. Application No.: 10/028,726 Page 10 ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser 180 -<del>-175 ---</del> GCA TTG-GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GCG Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly 195-190-GAA GTA TTA CAA ATC GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATC Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met <del>- 210</del> CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu 225 ----230 AAA CAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA GCT CGA Lys Clu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Cly Ser Pro Arg -245<del>- 240 -</del> ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Cly Cln Asn Arg Ser Ala Arg Ile Ala Lys Cln Leu 255 GAA AAT GAT ACA AGA ATT ATT GAA CTT CTC TGT AAA GAA CAT GAA TGT Clu Asn Asp Thr Arg Ile Ile Clu Val Leu Cys Lys Clu His Clu Cys <del>-270 - 275 -</del> AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT 1035 Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe 290 ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA -1083Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu 300 305 310 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA Asn Leu Ser Lys Arg Tyr Glu Clu Ile Tyr Leu Lys Asn Lys Asp Leu ______325 <del>---320</del> -GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Cln Thr Asp Ser _____340 335 ATA CAC ACT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp 350 <del>- 355</del>-GAA CAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met 370

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AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GA Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser As 380 385 385	<del>sp Gln</del>
CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AA Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val As 400 405	<del>on Pro</del>
AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC T Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Pl	TT AAA 1419 ne Lys
415 420 425	
GAG AAA TTT GCT AAA GCT CTG GGA CAG GGT TGT GTC GAA ATT GGGLU Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile G	<del>SA TCA 1467</del> l <del>y Ser</del>
CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG G	AA TCC 1515
Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met G 445 455	<del>lu Ser</del>
ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT CAA AAT TTT . Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe S	AGC AAA 1563
460 465 470	4 <del>75</del>
CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC G	CT CTT -1611
Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys A 480 485 4	<del>la Leu</del>
GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT C Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn L 495 500 505	TT GAT 1659 eu Asp
TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT A	AT TTA 1707
Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu A	.sii iicu
AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA G Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys A	CA GAA 1755 la Glu
<u>525</u> <u>530</u> <u>535</u>	•
GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT CGLY Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Company 545 550	<del>llu His</del>
CGA ATC ATG GAA TCC CTT CCA TGG CTC TCA GAT TCA CCT TTA T	TT GAT 1851
Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu I	570
CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC C	ETT GAA 1899 Seu Glu
585 580 585	

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TCT GCT TGT CCT CTT AAT Ser Ala Cys Pro Leu Asn ————————————————————————————————————	Leu Pro Leu Gln Ag	AT AAT CAC ACT GCA GCA sn Asn His Thr Ala Ala 600	<del>1947</del>
GAT ATG TAT CTT TCT CCT Asp Met Tyr Leu Ser Pro	-Val Arg Ser Pro Ly	AG AAA AAA GGT TCA ACT ys Lys Lys Gly Ser Thr 615	<del>1995</del>
ACG CGT GTA AAT TCT ACT Thr Arg Val Asn Ser Thr 620 625	Ala Ann Ala Glu T	CA CAA GCA ACC TCA GCC hr Gln Ala Thr Ser Ala 30 635	2043
TTC CAG ACC CAG AAG CCA Phe Gln Thr Gln Lys Pro	Leu Lys Ser-Thr S	CT CTT TCA CTC TTT TAT  er Leu Ser Leu Phe Tyr  650	<del>2091</del>
AAA AAA GTG TAT CGG CTA Lys Lys Val Tyr Arg Leu ————————————————————————————————————	Ala Tyr Leu Arg L	TA AAT ACA CTT TGT GAA eu Asn Thr Leu Cys Glu 665	<del>- 2139</del> .
CGC CTT CTG TCT GAG CAG Arg Leu Leu Ser Glu His	Pro Glu Leu Glu H	CAT ATC ATC TGG ACC CTT Lis Ile Ile Trp Thr Leu 680	<del>2187</del>
TTC CAG CAC ACC CTG CAC Phe Gln His Thr Leu Glr 685	<del>ı Asn Clu Tyr Clu</del> L	ETC ATG AGA CAC AGG CAT Leu Met Arg Asp Arg His 695	<del>2235</del>
•	G TGT TCC ATG TAT G	GGC ATA TGC AAA GTG AAG Gly Ile Cys Lys Val Lys	<del>2283</del>
AAT ATA GAC CTT AAA TT	- AAA ATC ATT GTA A	ACA CCA TAC AAG GAT CTT Thr Ala Tyr Lys Asp Leu	2331
CCT CAT CCT GTT CAG GAG	G ACA TTC AAA CGT C	CTT TTG ATC AAA CAA GAC Val Leu Ile Lys Glu Glu	<del>2379</del>
GAG TAT GAT TCT ATT AT.  Glu Tyr Asp Ser Ile Il.	e Val Phe Tyr Asn 9	FCG GTC TTC ATG CAG AGA Ser Val Phe Met Gln Arg760	2427
CTC AAA ACA AAT ATT TT	G CAG TAT GCT TCC / u Gln Tyr Ala Ser 7	ACC AGG CCC CCT ACC TTG Thr Arg Pro Pro Thr Leu	<del>2475</del>
TCA CCA ATA CCT CAC AT	T CCT CGA AGC CCT '	TAC AAG TTT CCT AGT TCA Tyr Lys Phe Pro Ser Ser 790 795	<del>2523</del>

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Page 13	
CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG AAG AGT	<del>2571</del>
Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser	
CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA	<del>2619</del>
Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro	
<del>815</del> 820 825	
AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG	<del> 2667</del>
Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu	
<del>830 835 840</del>	
THE REPORT OF THE COLUMN TWO AND ADD CAR COT COL	2715
AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	£115
<u>845</u> <u>850</u> <u>855</u>	
AAA AGA ACT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTC AAA AAA CTA	<del>- 2763</del>
Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu	
860 865 870 875	
CCC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC	<del>2811</del>
Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu	
880 885 890	•
	0.050
CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT	<del>2859</del>
Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr 895 900 905	
895	
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	<del>2907</del>
Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
<del>910 915 920</del>	
AAC AAC GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT	2962
	2,702
Asn Lys Glu Glu Lys 925	
GGATTCATTG TCTCTCACAG ATGTGACTGT AT	2994

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 10, at the end of the application.

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#### In the Claims:

Please amend claims 35, 39 and 40 as follows:

1. (Original) A method of controlling cancer suppression in a mammal having a cancer suppressing gene, comprising the steps of:

making a substantially duplicated genetic material corresponding to the genetic material of said gene, the substantially duplicated material selected from the group consisting of a cloned cancer suppressing gene, a modified or defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof; and

interchanging said duplicated genetic material and the cancer suppressing gene of the mammal.

- 2. (Original) A method of claim 1, wherein before said making a substantially duplicated genetic material, determining the chromosomal location of said cancer suppressing gene of the mammal.
- 3. (Original) A method of claim 1, wherein after said making a substantially duplicated genetic material, detecting the presence or absence of an inactive cancer suppressing gene of a tissue sample of the mammal to determine whether or not the tissue sample cancer suppressing gene is defective or absent.
- 4. (Original) A method of claim 3, wherein in response to a determination that the tissue sample cancer suppressing gene is either defective or absent, replacing a cancer suppressing gene of the mammal with its clone.

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5. (Original) A method of claim 3, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by measuring the amount of protein product of said cancer suppressing gene, of the tissue sample, bound by an antibody specific for said protein.

- 6. (Original) A method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by:
  - (a) labeling said tissue sample with radioactive isotope;
  - (b) lysing the labeled tissue;
- (c) reacting the protein product of said cancer suppressing gene with an antibody specific for said protein thereby forming a protein/antibody immunocomplex;
  - (d) autoradiographing the immunocomplex obtained in step (c); and
- (e) determining the presence or absence of the protein product by comparing the autoradiogram of step (d) with the autoradiogram of the standard protein product.
- 7. (Original) The method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by enzyme immunoassay techniques.
- 8. (Original) The method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by immunocytochemistry methods.
- 9. (Original) The method of claim 5, wherein the cancer suppressing gene is the RB gene and the protein product is ppRB¹¹⁰.

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- 10. (Original) The method of claim 1, wherein said cancer suppressing gene is replaced with substantially duplicated material selected from the group consisting of said cloned cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof, for therapeutic purposes.
- 11. (Original) The method of claim 1, wherein said cancer suppressing gene is replaced with substantially duplicated material selected from the group consisting of said defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof, for facilitating the testing of the carcinogenicity of environmental influences.
- 12. (Original) The method of claim 2, wherein the location of said cancer suppressing gene is determined by chromosome walking.
- 13. (Original) The method of claim 2, wherein the location of said cancer suppressing gene is determined through organic markers.
- 14. (Original) A method of claim 2, wherein:
  said chromosomal location of said cancer suppressing gene is determined
  by testing genes of a chromosome for phenotypic expression;

determining one of the genes of said chromosome to be a marker gene; and using chromosomal walking techniques to locate a cancer suppressing gene.

15. (Original) An animal genetically altered so as to have the allele of at least one cancer suppressing gene selected from the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a mixture thereof.

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16. (Original) An animal of claim 15, wherein said defective allele is selected from the group consisting of defective alleles of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homolgues thereof, fragments thereof, and mixtures thereof.

- 17. (Original) An animal of claim 15, wherein said allele contains a DNA fragment having at least one defective nucleotide sequence.
- 18. (Original) An animal of claim 15, wherein said defective allele contains a DNA fragment having at least one defective RB nucleotide sequence.
  - 19. (Original) The animal of claim 15, wherein said animal is a mouse.
- 20. (Original) A method for determining the carcinogenicity of suspected environmental influences, using the animal of claim 14, comprising the steps of:

  exposing said animal to a suspected environmental influence;

  observing the animal for the phenotypic expression of cancer; and determining carcinogenicity of the suspected environmental influence in response to observing a phenotypic expression of cancer in the animal.
- 21. (Original) A method of claim 20, wherein said exposing includes exposing to a source of radiation.
- 22. (Original) A method of claim 20, wherein said exposing includes exposing to tobacco combustion products.

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- 23. (Original) A method of claim 20, wherein said exposing includes exposing to food additives.
- 24. (Original) A method of claim 20, wherein said exposing includes exposing to artificial substances.
- 25. (Original) A method of claim 20, wherein said observing includes examining the animal for tumor development.
- 26. (Original) A method of claim 25, wherein in response to the formation of a tumor in the animal, analyzing the tumor for the presence of cancer cells.
- 27. (Original) A method of making the animal of claim 15, comprising: using at least one allele of an animal cancer suppressing gene selected from the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a mixture thereof;

mutating at least one animal cell with said allele to form a mutated cell; introducing said mutated cell into an animal blastocyst;

permitting growth of the blastocyst for a given period of time sufficient to incorporate said allele into its cells; repressing genetic recombinations within said cells; transferring the blastocyst containing said allele into the uterus of a pseudo pregnant animal for giving birth subsequently to an animal bearing said allele;

breeding said animal to reproduce additional animals; and selecting the animal of claim 14 from said additional animals by determining the presence therein of the said allele.

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28. (Original) A method of claim 27, wherein before introducing said allele, removing said blastocyst from a super ovulated animal, and wherein said blastocyst is comprised of undifferentiated cells.

- 29. (Original) A method of claim 27, wherein said introducing is performed in vitro.
- 30. (Original) A pharmaceutical composition wherein the active ingredient is selected from the group consisting of a naturally occurring intact cancer suppressing gene, a cloned intact cancer suppressing gene, fragments thereof, homolgues thereof and mixtures thereof.
- 31. (Original) A pharmaceutical composition of claim 30, wherein said naturally occurring and cloned cancer suppressing gene is selected from the group consisting of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homolgues thereof, fragments thereof, and mixtures thereof.
- 32. (Original) A pharmaceutical composition of claim 30, wherein the active ingredient is selected from the group consisting of RB cDNA, modified RB cDNA fragment, clones thereof, homologues thereof and mixtures thereof.
- 33. (Original) A pharmaceutical composition of claim 31, wherein the active ingredient for each of said gene is selected from the group consisting od cDNA of said gene, fragments of said cDNA, homologues thereof and mixtures thereof.

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34. (Original) A pharmaceutical composition of claim 32, wherein the

cancer suppressing gene is isolated from human chromosome 13 region 13q14.

35. (Currently amended) A pharmaceutical composition of claim 31, wherein the cancer suppressing gene and its clone each has the following nucleotide sequence comprising SEQ ID NO:1.:

TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTTGTAA CGGGAGTCGG GAGAGGACGG	60
GGCGTGCCCC GCGTCGCCCC GCGTCGTCCT CCCCGGCCCCT CCTCCACAGC TCGCTGGCTC	<del>- 120</del>
CCCCCCCCGA AACCCCTC ATC CCC CCC AAA ACC CCC CGA AAA ACC GCC GC	<del>171</del>
ACC GCC GCT GCC GCC GCC GCA CCC GCA CCC CCC CCC CCC	219
CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GA	<del>267</del>
CTC GTC ACC CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA  Leu Val-Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala  50 55	<del>315</del>
TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp 60 75	<del>- 363</del>
TTA ACT TGG GAG AAA GTT TCA TCT GTG GAT GGA GTA TTG GGA GGT TAT  Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr  80 85 90	411
ATT CAA AAC AAA AAC GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA  Ile Gln Lys Lys Lys Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Ala  ———————————————————————————————————	<del>459</del>
GTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn  110 115 120	<del>507</del>
ATA CAA ATC ACT CTC CAT AAA TTC TTT AAC TTA CTA AAA CAA ATT CAT  Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp  125 130 135	<del>555</del>

**PATENT** LEE et al. Application No.: 10/028,726 Page 21 ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAC AAG TAT 603 Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Lys Lys Tyr 145 ____150 _____ 140 ---GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu 160 170 ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT 699 Ile Tyr Leu Thr Cln Pro Ser Ser Ser Ile Ser Thr Clu Ile Asn Ser -175 ---180 GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly 190--<del>- 195 --</del> GAA CTA TTA CAA ATC CAA CAT CAT CTC CTC ATT TCA TTT CAC TTA ATC 795 Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met 210----215<del>205 ---</del> CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu 225 ____230___ AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA Lys Clu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Cly Ser Pro Arg <del>___240 ____ 245 _</del> ACA CCC ACG CGA GGT CAG AAC ACG AGT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu ______260 GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys 270 <del>---275</del> AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe ATC AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA Met Asn Ser Leu Cly Leu Val Thr Ser Asn Cly Leu Pro Clu Val Clu 310 305 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu 325 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser 340---

**PATENT** LEE et al. Application No.: 10/028,726 Page 22 ATA CAC ACT TTT CAA ACA CAG AGA ACA CCA CGA AAA ACT AAC CTT GAT Ile Asp Ser Phe Glu Thr Gln Arq Thr Pro Arg Lys Ser Asn Leu Asp <del>-350 --</del> GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG Glu Clu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met <del>365 370 375 375</del> AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln 380 -- 385 <del>--390----</del> CCT TCA GAA AAT CTC ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA -1371Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro <del>-400 -</del> 405---AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA CGA TAC ATC TTT AAA Lys Clu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys 420 <del>- 415 - -</del> GAG AAA TIT GCT AAA GCT GTG GGA CAG GCT TGT GTC GAA ATT GGA TCA 1467 Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser <del>-----435----</del> CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC Gln Arg Tyr Lys Leu Cly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser 445 450 ATC CTT AAA TCA GAA GAA CAA CGA TTA TCC ATT CAA AAT TTT AGC AAA - 1563 Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys <del>-470</del> 465 CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu _____485 480 GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT 1659 Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp ----500 TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA 1707 Ser Cly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu 515 -1755AAA GCC TIT GAT TIT TAC AAA GTG ATC GAA AGT TIT ATC AAA GCA GAA Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu 530 GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His 545 550

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CCA-	<u> አጥር</u>	ATG	CAA	TCC	CTT	CCA	TGG	CTC	TCA	GAT	TCA	ССТ	- <del>ΤΤ</del> Δ	· - <del>TTT</del>	-GAT-		<del>-1851</del>
			Glu														
_							-			_						*	,
Omm.	7 mm	7.7.7.	CI N N	TTC N	7 7 C	CAC	CCA	(17.7)	CCA	CCA	7 CT	C' እ T'	CAC	CTTTT	$C \Lambda \Lambda$		<del>-1899</del>
			Gln														1000
			575											БСС			
ጥረም	CCT	TCT	CCT	CTT.	7.7.7.	CTT	CCT	CTC	CAG	አልጥ	እ አ <del>፲</del>	-CAC	ACT		-CCA-		<del>- 1947</del>
			Pro													•	1517
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ACG-	CGT	GTA	AAT	TCT	ACT	-GCA	TAA	GCA	GAG	ACA	CAA	-GCA	ACC	TCA	-GCC-		<del>2043</del>
			Asn														
620			<del></del>		625					<del>-630</del>					- <del>635</del>		
TTC	CAC	ACC.	CAC	AAC	CCA-	TTC	ΔΛΔ.	TCT	ACC	TCT	СТТ	тсь	CTC	<u> Դ.Դ.Դ.</u>	тат.		2091
			-Gln														2002
				640					645	-				650			
		ama	m 2 m	aaa	Oma	aaa	m a m	ama	aaa	CITE N	7 7 17	7 (7)	cmm.	mani	(17.7		<del>2139</del>
			Tyr														<del>-2139</del>
			655											Cys	Oiu		
																<u> </u>	<del>2187</del>
			Ser										Trp	-Thr	- <del>Leu</del>		
		670					675					<del>-680</del>					
TTC	CAG	CAC	ACC	CTG	CAG	AAT	GAG	TAT	CAA	CTC	ATG	AGA	GAC	-AGC	CAT		<del>-2235</del>
			Thr									Arg	Asp	Arg	His		
	685					690					695						
TTG	GAC	-CAA	ATT	ATG	ATG	TCT	TCC	ATG	-TAT	GGC	ATA	-TGC	AAA	CTC	AAG-		2283
			Ile														
<u>א א די</u>	_ אידי א	-CAC	-CTT	<u> </u>	<u> </u>	444	ATC	Δጥጥ	-СТЪ	ACA	CCA	-TAC	AAG	CAT	CTT		<del>2331</del>
			-Leu			-											
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															Glu		<del>2379</del>
			735											-+u			
																	<del>2427</del>
Glu	Tyr	Asp	ser	11c	- 11e	·va⊥	rne	Tyr	- <del>ASN</del>	- <del>ser</del>	-va1	-rne	- MEE	<del>-uin</del>	Arg		

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Page 24	
TG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG	<del>2475</del>
eu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu	
765 770 775	
CA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA	<del>2523</del>
er Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser	
80 785 790 795	
GG TEN GGG NEW GOT GGN GGG NNG NEG MAR ARE MGN GGG CEC NAC ACE	<del>2571</del>
CC TTA CCC ATT CCT GGA GCC AAC ATC TAT ATT TCA CCC CTC AAG ACT	25/1
Pro Leu Arg Ile Pro Cly Cly Asn Ile Tyr Ile Ser Pro Leu Lys Ser	
CA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA	<del>2619</del>
ro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro	
815 820 825	
GA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG	<del>2667</del>
Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu	2007
830 835 840	
AG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC ACC GAC CGT GTG CTC	<del>2715</del>
Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	
845 850 855	
AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA	<del>2763</del>
Lys Arg Ser Ala Clu Cly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu	
865 870 875	
	<del>2811</del>
CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu	ZOTT
880 895 890	
CA GGA GAG TCC AAA TTT CAG CAG AAA CTG GGA GAA ATG ACT TCT ACT	<del>2859</del>
Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr	
895 900 905	
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	<del>- 2907</del>
Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
910 915 920	
TO THE TAX AND THE	2062
AAC AAC CAA CAC AAA TGACGATCTC ACGACCTTCC TGGACACTGT GTACACCTCT	2302
<del>Asn Lys Glu Glu Lys</del> <del>925</del>	
GATTCATTC TCTCTCACAC ATCTGACTGT AT	<del>2994</del>

36. (Original) A pharmaceutical composition of claim 32, wherein said RB cDNA fragment is selected from the group consisting of RB-1, RB-2, RB-5,  $_y$ 79R8 and mixtures thereof.

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- 37. (Original) A pharmaceutical composition of claim 32, wherein a resulting mRNA transcript of said RB cDNA fragment has 4.6 kb.
- 38. (Original) A pharmaceutical composition of claim 37, wherein the cloned genomic DNA has at least 27 exons.
- 39. (Currently amended) A pharmaceutical composition of claim 30, wherein the cloned RB cDNA transcribes into mRNA which translates in protein having an amino acid sequence comprising SEQ ID NO:2.÷

<u>MPPKTPRKTAATAAAAAAEPPAPPPPPPEEDPE</u> QDSGPEDLPLVRLEFEETEEPDFTALCQKLKIPDH, VRERA WLTWEKVSSVDGVLGGYIOKKKELWGICIFIAAVDLDEMS FTFTELOKNIEISVHKFFNLLKEIDTSTKVDNAMSRLLKK YDVLFALFSKLERTCELIYLTQPSSSISTEINSALVLKVS WITFLLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML LKEPYKTAVIPINGSPRTPRRGOMRSARIAKOLENDTRII EVLCKEHECNIDEVKNVYFKNFIPFMNSLGLVTSNGLPEV ENLSKRYEEIYLKNKDLDARLFLDHDKTLQTDSIDSFETQ RTPRKSNLDEEVNVIPPHTPVRTVMNTIQQLMMILNSASD <del>OPSENLISYFNNCTVNPKESILKRVKDICYIFKEKFAKA</del>V **CQCCVEICSORYKLGVRLYYRVMESMLKSEEERLSIQNFS KLLNDNIFHMSLLACALEVVMATYSRSTSQNLDSGTDLSF PWILNVLNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE** HRIMESLAWLSDSPLFDLIKQSKDREGPTDHLESACPLNL PLONNHTAADMYLS PVRS PKKKCSTTRVNS TANAETQATS AFQTQKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP **ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV** <u>KNIDLKFKIIVTAYKDLPHAVQETFKRVLIKEEEYDSIIV</u> FYNSVFMQRLKTNILQYASTRPPTLSPIPHIPRSPYKFPS SPLRIPCCNIYISPLKSPYKISECLPTPTKMTPRSRILVS <del>(834)</del> **ICESFCTSEKFOKINOMVCNSDRVLKRSAEGSNPPKPLKK** (874) **LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ** <del>(928)</del> KMNDSMDTSNKEEK

single letter abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His;

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I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

# 40. (Currently amended) A DNA nucleotide sequence comprising SEQ

# <u>ID NO:1.</u>÷

FTCCCCTT	TT-1	CTCI	<del>/CCC</del>	SA CO	TTG/	\AAT'	r-AT	r <del>rrr</del> (	TAA	-eec	SACT	e <del>cc</del> -(	SAGA	GACG	3	60
GCGTGCC	cc-c	CCTC	GCGCG	C GC	CGTC	TCC	r-cc	CCCC	CCT-	-CCT	SCAC.	AGC-'	rece:	FGGCT	c	-120
ecccccc	GA -I	AGGG	GTC	ATC	-ccc	CCC	AAA	ACC	-CCC	CGA	AAA	-ACC	GCC	-GCC-		<del>-1</del> 71
			<del></del>	Met	Pro	Pro	Lys	Thr	Pro	Arg	Lys	Thr	Ala	Ala		
<del></del>		<del>,</del> -														
ACC CCC	GCC	CCT	GCC	-GCC	GCG	GAA	-ecc	CCC	GCA	CCG	-CCC	-CCG	-ccg	-ccc-		219
Thr Ala													Pro	Pro		
		-15	<del>.</del>		<del>.</del>		20					<del>25</del>			•	
CCT-CCG-	TAG	GAG	GAC	-CCA-	GAG	CAG	GAC	AGC	GGC	-ccc	GAG	GAC	CTG	-CCT		26
ro Pro																
	-30	<del></del>	<del></del> -	<u> </u>		-35				<del></del>	40	_				
CTC GTC	AGG-	CTT	GAG	TTT	GAA	GAA	ACA	GAA	CAA	CCT	CAT	TTT	ACT	GCA	,	<del>-31</del>
eu Val	Arq	Leu	Glu	Phe	Glu	Glu	Thr	Glu	Clu	Pro	Asp	-Phe	Thr	Ala		
45											_				• .	
FTA TGT	CAC	AAA	TTA	AAG	ATA	CCA	CAT	CAT	GTC	AGA	GAG	AGA	CCT	TGG		<del>-36</del>
<del>Leu Cys</del>	Cln-	Lys-	Leu	Lys-	Ile	Pro	Asp	His	Val	Arg	Glu	-Arg	Ala	Trp		
60		<del></del>		<del>- 6</del> 5		<del></del> -,			<del>70</del>					<del>75</del>		
TA ACT	TGG	GAG	AAA	CTT	TCA	TCT	CTC	GAT	GGA	GTA	TTC	-GGA	-GGT	TAT		-41
Leu Thr	Trp	Glu	Lys	Val-	Ser	Ser	Val	Asp	Gly	-Val	Leu	Gly	<del>-Cly</del>	<del>-Tyr</del>		
<del></del>		<del></del>	- 80	·				85					90			
TT CAA	AAG	AAA	AAC	-GAA-	CTG	TCC	GGA	ATC	TGT	ATC	TTT	ATT	-GCA	GCA		-45
I <del>le C</del> ln-																*
		_95					100			<del></del> :		105				
GTT GAC	CTA-	CAT	GAC	ATC	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC-		<del>-5</del> 0
Val Asp																
													-			
TA CAA	ATC	AGT	GTC	CAT	AAA	TTC	TTT	AAC	TTA	CTA	AAA	-GAA	TTA-	GAT		<del>55</del>
Ile Glu																
125											-			-		

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Page 27														•	
ACC ACT	ACC	AAA-	GTT	CAT	AAT	GCT	ATG-	TCA	AGA	CTC	TTC	AAG	AAG	TAT	<del>603</del>
Thr Cor	Thr	T.370	$V_2$ 1	Δan	Agn	Ala	Met-	Ser	Ara-	Leu	Leu	Lys	Lys-	Tyr	
140		-1-		145			<del></del>		150			<del></del>		<del>155</del>	
															<del>651</del>
Asp Val	1 1 C	Dho	71a	LOU	Dho	Cor	Lva	I.C.I.	Clu	Ara	Thr	Cvs	Clu	Leu	
<del>ASP var</del>	ь <del>еи</del>	-rnc	160-					165		3			170		
A <del>TA TAT</del>				~~~		7 CF	maa	7 (11 )	ጥረም	л СТ	CAA.	አጥአ	አልጥ	TCT	<del>699</del>
A <del>TA TAT</del> Ile Tyr	TTG	ACA	CAA	-CCC	ACC	Cox	Cor	Tla	Cor	Thr	Cli	Tle	Agn-	Ser	0.5 2
Ile Tyr	ьeu	175	<del>Gin</del>	140	-SCI	DC1	180	-110				185		-	•
														aaa	747
CCA TTG	<del>-GTC</del>	CTA	AAA	GTT	TCT	TGC	ATC	-ACA	TTT	TTA	-'I''I'A	- GCT	TAAA	Clar	<del>747</del>
Ala Leu	-Val	Leu	-Lys	Val	Ser	-Trp	- <del>IIe</del>	Thr	Phe	ьеu	<u></u>	Ald	TAR.	- <del>оту</del>	
										-					
CAA CTA	тта	-CAA	ATG	CAA	GAT	CAT	CTG	CTG	ATT	TCA	TTT	CAC	TTA	ATG	795
Clu Val	Leu	Gln	Met	- Clu	Asp	Asp	Leu	-Val	Ile	Ser	-Phe	<del>-Gln</del>	Leu	-Met	
205					210	,				215		•		•	
ama mam	OIII O	- Crorr	CNC	ጥለጥ	dididi.	ע ייייט	<u> </u>	_стс	тса	CCT	CCC	ATC	TTG	CTC-	843
<del>CTA TOT</del> Leu Cys	Val	Lau	-Nan	Tur	_Dbc	Tle	T.va	-Leu	-Ser	-Pro	Pro	-Met	Leu	-Leu	
<del>220</del>	vai	БСС	- qan	225					<del>-230</del>	<del></del>	<del></del>		, ,	<del>235</del>	
															891
AAA CAA Lys Clu	- CÇA	mvr-	L	Thr	Ala	Val	Tle	Pro	Tle	- Asn	Glv	Ser	Pro	-Arq	
<del>ys Giu</del>		) 1 <u>y 1</u>	— <del>1175</del> — <del>240</del>	1111	HIU	· vai		245					<del>-250</del>		
															020
ACA CCC	AGG	- CGA	GGT	- CAC	-AAC	ACC	AGT	GCA	~ <del>CGG</del>	ATA	ν 1 -	Tird	Cln	Lou	9 <del>39</del>
Thr Pro	Are	Arg	Gly	-G1n	- Asn	-Arg	- <del>Ser</del>	Ala	Arg	<del>-110</del>	Alc	<del>у-</del> 5			
															.*
GAA AAT	GAT	- ACA	AGA	ATI	TTA	GAA	GTT	CTC	TGT	' AAA	-GAF	CAT	-GAA	TGT	<del>987</del>
Glu Agn	Agr	Thr	Are	Ile	·Ile	- Glu	-Val	. Leu	⊢ <del>Cys</del>	⊢- <del>Lys</del>	$-G1\iota$	ı His	– <del>Gl⊍</del>	<del>Cys</del>	
	<del>27</del> (	)				<del>27</del> 5				· ·	280	<del>)</del>			
AAT ATA	מאי	r cac	CTC	י אארי	רב.ב		TAT	TTC	: AAA	LAA -	TT	ATA	CCT	TTT	1035
Asn Ile	\ \Acr	- GA	. Val	_ I.v.	- Agr	. Val	TVX	-Phe	- Lys	Asr	Phe	· Ilc	Pre	- Phe	
<del>- 285</del>					29(	)				295	<del>,</del> .				
			_ ~~-	- ami		N 70 71 71	m/dn	ח אא ח		, Cara		CAC	:_CT7	CAA	1083
ATG AAT Met Asr	TC'	r CT	- CGA	1 CT	. 172 1	1 ACA	COL	· Aar	Cla	- C.	Pre	Gli	. Val	Glu	
Met Asr	ı se	<del>г ье</del> ι	1 G13	<del>- 30</del> 5	<del>. va.</del>				- 31(	)——				<del>- 315</del>	
AAT CT	TC	r AA	A CGI	ATA(	CA/	<del>\ GA/</del>	AT7	r TAT	F CTT	r AA	AA'	r AA/	<del>\ GA</del> :	L-CTA	1131
Aan Lai		r Iv	1 Arc	TVI	-Gh	$_{1-Glt}$	1 Il	<del>-Ty</del> i	<u>Leι</u>	<del>ı Ьу:</del>	3 Ası	<del>а - Ьус</del>	S ASI	<del>. ьeu</del>	
			-32(	)	<del></del> -			- 34	,				9.54	,	
arm aa.		у шил.	v umumur	יייים יו	י מים	<u> ር</u> ያ	ר כיסי	г да	<u> Α - Α - Γ</u>	r Crr	r CA	3 AC	r GA	r TCT	1179
Asp Ale	1 AU	a I e	_ II	_ I e	. Δα	n Hir	<u> </u>	 - J.V!	Th	r Lei	ı Cl	n-Th:	c Ası	ser	:

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Page 28	
ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp	<del>1227</del>
350 355 360	
CAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met	<del>- 1275</del>
<del>365</del> <del>370</del> <del>375</del>	
AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA Asn Thr Ile Gln Cln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln	<del>- 1323</del> »
380 385 390 395	
CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro	<del>1371</del>
400 405 410	
AAA CAA AGT ATA CTG AAA AGA GTG AAG CAT ATA GGA TAC ATC TTT AAA Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys	<del>- 1419</del>
415 420 425	
	1467
GAG AAA TTT CCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser	
<u>440</u>	
CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC	<del>1515</del>
CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAT TGG Gln Arg Tyr Lys Leu Cly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser	
445 450 455	ř
ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA	<del>- 1563</del>
Mot Low Lyg Sor Cly Cly Cly Arg Ley Ser Ile Cln Asn Phe Ser Lys	
460 465 470 475	
CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT	1611
Lou Lou Agn Agn Agn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu	
480 485 490	
GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT	<del>1659</del>
Gla Wal Wal Mot Ala Thr Tyr Ser Arg Ser Thr Ser Gla Asa Leu Asp	1
495 500 505	
TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA	<del>1707</del>
Sor Cly Thr Agn Lou Sor Phe Pro Trp Ile Leu Asn Val Leu Asn Leu	
510 515 520	
AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA	<del>1755</del>
Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu  525 530 535	
CCC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT	<del>1803</del>
Cly Agn Low Thr Arg Clu Met Ile Lys His Leu Glu Arg Cys Glu His	
540 545 550 555	

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CGA ATC ATG GAA TCC CTT GCA TGG CTC TCA GAT TCA CCT TTA TTT GAT Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp	1851
CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA  Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu  575 580 585	<del>1899</del>
TCT GCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA  Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala  595 595	1947
GAT ATG TAT CTT TCT CCT GTA AGA TCT CCA AAG AAA AAA GGT TCA ACT  Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Cly Ser Thr  605 610 615	<del>1995</del>
ACG CGT GTA AAT TCT ACT GCA AAT GCA GAG ACA CAA GCA ACC TCA GCC  Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala  620 635	2043
TTC-CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTC TTT TAT  Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr  640 645	<del>2091</del>
AAA AAA GTG TAT CGG CTA GCC TAT CTC CGG CTA AAT ACA CTT TGT GAA Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu 655	<del>- 2139</del>
CGC CTT CTG TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT  Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu  670 675 680	<del>2187</del>
TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT  Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His  685 690 695	<del>2235</del>
TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG  Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys  700 705 710 715	<del>2283</del>
AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu 720 725	<del>2331</del>
CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG Pro His Ala Val Glu Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu  735 740 745	<del>- 2379</del>
GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA  Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg  750 755	2427

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CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG	<del>2475</del>
Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu	
765 770 775	
TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA	2523
Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser	•
780 785 790 795	
CCC TTA CGC ATT CCT GGA GGC AAC ATC TAT ATT TCA CCC CTG AAG AGT	2571
Dro Leu Arg Ile Pro Cly Cly Asp Ile Tyr Ile Ser Pro Leu Lys Ser	
800 805 810	
CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA	2619
Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro	
<del>815 820 825</del>	
AGA TCA AGA ATC TTA GTA TGA ATT GGT GAA TCA TTC GGG ACT TCT CAG	2667
Arg Ser Arg Ile Leu Val Ser Ile Gly Clu Ser Phe Gly Thr Ser Clu	
830 835 840	
AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC	2715
Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	
<del>845 850 855</del>	
AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA	2763
<del>Lys Arg Ser Ala Clu Cly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu</del>	
860 865 870 875	
CCC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC	2811
Arg Phe Asp Ile Clu Cly Ser Asp Clu Ala Asp Cly Ser Lys His Leu	
	٠.
CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT	2859
Pro Gly Clu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr	
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	<del>2907</del>
Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
<del>910915920</del>	,
AAC AAC GAA GAC AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT	2962
Asn Lys Glu Glu Lys	
<del>925</del>	
GGATTCATTG TCTCTCACAG ATGTGACTGT AT	2994

41. (Original) A method of therapeutically treating inactive, mutative or absent cancer suppressing genes comprising:

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treating said inactive, mutative or absent cancer suppressing genes with at least a portion of intact cancer suppressing genes.

- 42. (Original) A method of claim 41, wherein said cancer suppressing genes are each a substance selected from the groups consisting of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, and mixtures thereof.
- 43. (Original) A method of claim 41, wherein said treating includes: treating said inactive, mutative or absent cancer suppressing gene with a substance selected from the group consisting of an RB gene, a portion of said gene, or a mixture thereof.
- 44. (Original) A method of claim 43, wherein said portion is selected from the group consisting of RB cDNA, RB cDNA fragment, homologues thereof and mixtures thereof.
- 45. (Original) The method of claim 41, wherein the intact cancer suppressing gene, or portion thereof, is delivered to the site of a tumor by means of a retrovirus.
- 46. (Original) A method of claim 41, wherein the intact cancer suppressing gene, or a portion thereof, is delivered to the site of a tumor by a liposome.
- 47. (Original) A method of claim 41, wherein the location of said cancer suppressing gene is determined by utilizing a genetic marker.

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47. (Previously added) A method of suppressing the neoplastic phenotype of a cancer cell, the method comprising contacting the cell with a nucleic acid encoding a full length, wild type retinoblastoma protein.

#### **REMARKS**

The amendments to the nucleotide sequence in "Table 4" and claims 35 and 40 correct errors of a typographical nature made without deceptive intent. The codons at nucleotide positions 223-225 (CCT), encoding "Pro", and 226-228 (GAG), encoding "Glu", were present in the original sequence from informal Figure 9 of the parent application, 08/472,760, filed November 27,1996, a copy of which is enclosed for the convenience of the Examiner. These codons were inadvertently changed to "CCG" and "TAG" in the present application. That this is inadvertent error is supported by the fact that, under "TAG" at positions 226-228, which encodes a stop codon, the originally-encoded amino acid "E" (Glu) appears in "TABLE 4" of the Specification submitted on December 21, 2001, and "Glu" again appears in the Substitute Specification submitted April 30, 2002, in response to the Notice to File Corrected Application Papers, mailed January 31, 2002.

The Sequence Listing submitted for Application No. 08/472,760, filed November 27,1996, does not contain these inadvertent errors and, thus, the amendments to the Specification and Claims now seek to conform to the nucleotide sequence present in the Sequence Listing of the parent application.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. The information contained in the computer readable form of Application No. 08/472,760 was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy, a copy of which is enclosed for the convenience of the Examiner. This amendment contains no new matter.